

Page 78, /line 23, delete "phosphotase" and insert  
--phosphatase--.

Page 79, line 20, after "Implants" and before  
"included", insert --that--.

Page 82, line 22, after "group" delete "II" and insert  
--I--.

Duplicate pages effecting these changes for placement  
in the file of the Patent Office are included for the  
convenience of the Examiner.

In the Claims

Delete claims 27, 30, 31, 47 through 49, 52 through  
57, and 80.

Amend the remaining claims as follows:

21. (Amended) Osteogenic protein, produced by expression  
of recombinant DNA in a host cell, said osteogenic protein  
comprising a pair of polypeptide chains and capable of inducing  
endochondral bone formation in association with a matrix when  
implanted in a mammal.

*Sub*  
*141*  
*65*  
*Cont*  
*a*

<sup>1</sup>/<sub>22</sub>. (Amended) A protein, produced by expression of recombinant DNA in a host cell[,] <sup>*substantially free of other copolymerizing proteins*</sup> and comprising [one or more] a pair of polypeptide chains, each of which has less than about 200 amino acids [long] in a sequence sufficiently duplicative of the sequence of COP-5 or COP-7 such that said pair of polypeptide chains, when <sup>*disulfide*</sup> ~~disulfide~~ bonded to produce a dimeric species, has a conformation [protein is] capable of inducing bone or cartilage formation in association with a matrix when implanted in a mammal.

Claim 23, line 2, before "molecular weight", delete "an apparent" and insert --a--.

Claim 25, line 2, before "molecular weight", delete "an apparent" and insert --a--.

Claim 26, line 1, delete "22" and insert --21--.

*B6*  
*a*

<sup>10</sup>/<sub>45</sub>. ~~(Amended)~~ The protein of claims ~~21 or~~ <sup>*1*</sup>/<sub>22</sub> comprising the product of expression of a DNA in a procaryotic host cell.

*141*  
*141*

46. (Amended) A protein expressed from a genomic DNA sequence encoding an amino acid sequence sufficiently duplicative of that of the sequence encoded by the gene of

*94*

BB, cont  
Figure 1A such that said encoded sequence, in dimeric form, induces bone or cartilage formation when implanted in a mammal in association with a matrix.

B2  
50. (Amended) [A cell line engineered to express] The protein of claim ~~21~~ <sup>12</sup> ~~or~~ <sup>22</sup> produced by expression in a mammalian cell line.

51. (Amended) The protein of claim ~~21~~ <sup>12</sup> ~~or~~ <sup>22</sup> having a half-maximum bone forming activity of at least about 20-25 ng per 25 mg of implant. 14

Add the following claims:

B8  
79-54  
13  
51. The protein of claim ~~21~~ <sup>1</sup> ~~or~~ <sup>22</sup> comprising the amino acid sequences:

10 20 30  
CX<sub>1</sub>RX<sub>2</sub>X<sub>3</sub>LX<sub>4</sub>VX<sub>5</sub>FX<sub>6</sub>DX<sub>7</sub>GWX<sub>8</sub>X<sub>9</sub>WX<sub>10</sub>X<sub>11</sub>X<sub>12</sub>PX<sub>13</sub>GX<sub>14</sub>X<sub>15</sub>AX<sub>16</sub>YC

40 50  
X<sub>17</sub>GX<sub>18</sub>CX<sub>19</sub>X<sub>20</sub>PX<sub>21</sub>X<sub>22</sub>X<sub>23</sub>X<sub>24</sub>X<sub>25</sub>X<sub>26</sub>X<sub>27</sub>X<sub>28</sub>NHAX<sub>29</sub>X<sub>30</sub>QX<sub>31</sub>

60 70  
X<sub>32</sub>VX<sub>33</sub>X<sub>34</sub>X<sub>35</sub>NX<sub>36</sub>X<sub>37</sub>X<sub>38</sub>X<sub>39</sub>PX<sub>40</sub>X<sub>41</sub>CCX<sub>42</sub>PX<sub>43</sub>X<sub>44</sub>X<sub>45</sub>X<sub>46</sub>

80 90  
X<sub>47</sub>X<sub>48</sub>X<sub>49</sub>X<sub>50</sub>LX<sub>51</sub>X<sub>52</sub>X<sub>53</sub>X<sub>54</sub>X<sub>55</sub>X<sub>56</sub>X<sub>57</sub>VX<sub>58</sub>LX<sub>59</sub>X<sub>60</sub>YX<sub>61</sub>X<sub>62</sub>M

100  
X<sub>63</sub>VX<sub>64</sub>X<sub>65</sub>CX<sub>66</sub>CX<sub>67</sub>,

wherein  $X_1=(K \text{ or } R)$ ;  $X_2=(H, R, \text{ or } K)$ ;  $X_3=(P, S, E \text{ or } Q)$ ;  $X_4=(Y, K \text{ or } F)$ ;  $X_5=(D, S \text{ or } E)$ ;  $X_6=(R, S, K \text{ or } A)$ ;  $X_7=(V, L, \text{ or } I)$ ;  $X_8=(N, Q, D \text{ or } S)$ ;  $X_9=(D, E \text{ or } N)$ ;  $X_{10}=(I \text{ or } V)$ ;  $X_{11}=(I \text{ or } V)$ ;  $X_{12}=(A \text{ or } S)$ ;  $X_{13}=(P, E, L \text{ or } K)$ ;  $X_{14}=(Y \text{ or } F)$ ;  $X_{15}=(H \text{ or } D)$ ;  $X_{16}=(F, Y \text{ or } N)$ ;  $X_{17}=(H, E \text{ or } S)$ ;  $X_{18}=(E \text{ or } A)$ ;  $X_{19}=(P, A \text{ or } Q)$ ;  $X_{20}=(F \text{ or } Y)$ ;  $X_{21}=(L, M \text{ or } I)$ ;  $X_{22}=(A, P \text{ or } T)$ ;  $X_{23}=(D, E \text{ or } K)$ ;  $X_{24}=(H \text{ or } S)$ ;  $X_{25}=(L, M \text{ or } F)$ ;  $X_{26}=(N \text{ or } K)$ ;  $X_{27}=(S, A \text{ or } P)$ ;  $X_{28}=(T \text{ or } S)$ ;  $X_{29}=(I, V, \text{ or } T)$ ;  $X_{30}=(V, I \text{ or } L)$ ;  $X_{31}=(T \text{ or } S)$ ;  $X_{32}=(L \text{ or } I)$ ;  $X_{33}=(N, H \text{ or } R)$ ;  $X_{34}=(S, A, F \text{ or } N)$ ;  $X_{35}=(V \text{ or } I)$ ;  $X_{36}=(P \text{ or } S)$ ;  $X_{37}=(G \text{ or } E)$ ;  $X_{38}=(K, Q, T \text{ or } S)$ ;  $X_{39}=(I \text{ or } V)$ ;  $X_{40}=(K \text{ or } E)$ ;  $X_{41}=(A, P \text{ or } S)$ ;  $X_{42}=(V \text{ or } A)$ ;  $X_{43}=(T \text{ or } E)$ ;  $X_{44}=(E, Q \text{ or } K)$ ;  $X_{45}=(L \text{ or } M)$ ;  $X_{46}=(S, N \text{ or } D)$ ;  $X_{47}=(A, S \text{ or } P)$ ;  $X_{48}=(I, L \text{ or } V)$ ;  $X_{49}=(S \text{ or } A)$ ;  $X_{50}=(M, I \text{ or } V)$ ;  $X_{51}=(Y \text{ or } F)$ ;  $X_{52}=(L, F \text{ or } Y)$ ;  $X_{53}=(D \text{ or } N)$ ;  $X_{54}=(E, D \text{ or } N)$ ;  $X_{55}=(N \text{ or } Q)$ ;  $X_{56}=(E, D, S \text{ or } K)$ ;  $X_{57}=(N \text{ or } K)$ ;  $X_{58}=(V \text{ or } I)$ ;  $X_{59}=(K \text{ or } R)$ ;  $X_{60}=(N, K \text{ or } H)$ ;  $X_{61}=(Q, E, R \text{ or } P)$ ;  $X_{62}=(D, E \text{ or } N)$ ;  $X_{63}=(V \text{ or } T)$ ;  $X_{64}=(E, D \text{ or } R)$ ;  $X_{65}=(G, A, S \text{ or } E)$ ;  $X_{66}=(G \text{ or } H)$ ; and  $X_{67}=(R \text{ or } H)$ .

<sup>14</sup>  
82. The protein of claim ~~21~~ <sup>1</sup> or ~~22~~ comprising the amino acid sequences:

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LX<sub>1</sub>VX<sub>2</sub>FX<sub>3</sub>DX<sub>4</sub>GWX<sub>5</sub>X<sub>6</sub>WX<sub>7</sub>X<sub>8</sub>X<sub>9</sub>PX<sub>10</sub>GX<sub>11</sub>X<sub>12</sub>AX<sub>13</sub>YC

X<sub>14</sub>GX<sub>15</sub>CX<sub>16</sub>X<sub>17</sub>PX<sub>18</sub>X<sub>19</sub>X<sub>20</sub>X<sub>21</sub>X<sub>22</sub>X<sub>23</sub>X<sub>24</sub>X<sub>25</sub>NHAX<sub>26</sub>X<sub>27</sub>QX<sub>28</sub>

X<sub>29</sub>VX<sub>30</sub>X<sub>31</sub>X<sub>32</sub>NX<sub>33</sub>X<sub>34</sub>X<sub>35</sub>X<sub>36</sub>PX<sub>37</sub>X<sub>38</sub>CCX<sub>39</sub>PX<sub>40</sub>X<sub>41</sub>X<sub>42</sub>X<sub>43</sub>

X<sub>44</sub>X<sub>45</sub>X<sub>46</sub>X<sub>47</sub>LX<sub>48</sub>X<sub>49</sub>X<sub>50</sub>X<sub>51</sub>X<sub>52</sub>X<sub>53</sub>X<sub>54</sub>VX<sub>55</sub>LX<sub>56</sub>X<sub>57</sub>YX<sub>58</sub>X<sub>59</sub>M

X<sub>60</sub>VX<sub>61</sub>X<sub>62</sub>CX<sub>63</sub>CX<sub>64</sub>,

wherein X<sub>1</sub>=(Y, K or F); X<sub>2</sub>=(D, S or E); X<sub>3</sub>=(R, S, K or A);  
X<sub>4</sub>=(V, L, or I); X<sub>5</sub>=(N, Q, D or S); X<sub>6</sub>=(D, E or N); X<sub>7</sub>=(I or  
V); X<sub>8</sub>=(I or V); X<sub>9</sub>=(A or S); X<sub>10</sub>=(P, E, L or K); X<sub>11</sub>=(Y or F);  
X<sub>12</sub>=(H or D); X<sub>13</sub>=(F, Y or N); X<sub>14</sub>=(H, E or S); X<sub>15</sub>=(E or A);  
X<sub>16</sub>=(P, A or Q); X<sub>17</sub>=(F or Y); X<sub>18</sub>=(L, M or I); X<sub>19</sub>=(A, P or T);  
X<sub>20</sub>=(D, E or K); X<sub>21</sub>=(H or S); X<sub>22</sub>=(L, M or F); X<sub>23</sub>=(N or K);  
X<sub>24</sub>=(S, A or P); X<sub>25</sub>=(T or <sup>S</sup>~~A~~); X<sub>26</sub>=(I, V, or T); X<sub>27</sub>=(V, I or  
L); X<sub>28</sub>=(T or S); X<sub>29</sub>=(L or I); X<sub>30</sub>=(N, H or R); X<sub>31</sub>=(S, A, F or  
N); X<sub>32</sub>=(V or I); X<sub>33</sub>=(P or S); X<sub>34</sub>=(G or E); X<sub>35</sub>=(K, Q, T or  
S); X<sub>36</sub>=(I or V); X<sub>37</sub>=(K or E); X<sub>38</sub>=(A, P or S); X<sub>39</sub>=(V or A);  
X<sub>40</sub>=(T or E); X<sub>41</sub>=(E, Q or K); X<sub>42</sub>=(L or M); X<sub>43</sub>=(S N or D);  
X<sub>44</sub>=(A, S or P); X<sub>45</sub>=(I, L or V); X<sub>46</sub>=(S or A); X<sub>47</sub>=(M, I or V);  
X<sub>48</sub>=(Y or F); X<sub>49</sub>=(L, F or Y); X<sub>50</sub>=(D or N); X<sub>51</sub>=(E, D or N);  
X<sub>52</sub>=(N or Q); X<sup>53</sup>=(E, D, S or K); X<sub>54</sub>=(N or K); X<sub>55</sub>=(V or I);  
X<sub>56</sub>=(K or R); X<sub>57</sub>=(N, K or H); X<sub>58</sub>=(Q, E, R or P); X<sub>59</sub>=(D, E or  
N); X<sub>60</sub>=(V or T); X<sub>61</sub>=(E, D or R); X<sub>62</sub>=(G, A, S or E); X<sub>63</sub>=(G or  
H); and X<sub>64</sub>=(R or H).

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83. The protein of claim 46 comprising the amino acid sequence:

OP1 1 10 20 30 40  
 LYVSFRDLGWQDWIIAPEGYAAYYCEGECAPPLNS  
 50 60 70  
 YMNATNHAIVQTLVHFINPETVPKPCCAPTQLNA  
 80 90 100  
 ISVLYFDDSSNVILKKYRNMVVRACGCH

84. The protein of claim 46 comprising the amino acid sequence:

OP1 1 10 20 30 40  
 CKKHELYVSFRDLGWQDWIIAPEGYAAYYCEGECAPPLNS  
 50 60 70  
 YMNATNHAIVQTLVHFINPETVPKPCCAPTQLNA  
 80 90 100  
 ISVLYFDDSSNVILKKYRNMVVRACGCH

15  
 85. *, substantially free of other contaminating proteins*  
 A protein comprising the amino acid sequence:

OP1 1 10 20 30 40  
 LYVSFRDLGWQDWIIAPEGYAAYYCEGECAPPLNS  
 50 60 70  
 YMNATNHAIVQTLVHFINPETVPKPCCAPTQLNA  
 80 90 100  
 ISVLYFDDSSNVILKKYRNMVVRACGCH

16  
 86. *, substantially free of other contaminating proteins*  
 A protein comprising the amino acid sequence:

OP1 1 10 20 30 40  
 CKKHELYVSFRDLGWQDWIIAPEGYAAYYCEGECAPPLNS  
 50 60 70  
 YMNATNHAIVQTLVHFINPETVPKPCCAPTQLNA  
 80 90 100  
 ISVLYFDDSSNVILKKYRNMVVRACGCH

BB  
 Cont

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87. A dimeric protein comprising the amino acid sequence:

CBMP-2a

1	10	20	30	40
CKRHPLYVDFSDVGWNDWIVAPPGYHAFYCHGECFPFLAD				
	50	60	70	
HLNSTNHAIVQTLVNSVNSKIPKACCVPTLSA				
80	90	100		
ISMLYLDENEKVVVLKQDMVVEGCGCR				

88. A dimeric protein comprising the amino acid sequence:

CBMP-2b

1	10	20	30	40
CRRHSLYVDFSDVGWNDWIVAPPGYQAFYCHGDCFPFLAD				
	50	60	70	
HLNSTNHAIVQTLVNSVNSSIPKACCVPTLSA				
80	90	100		
ISMLYLDEYDKVVVLKQEMVVEGCGCR				

89. A dimeric protein comprising the amino acid sequence:

CBMP-3

1	10	20	30	40
CARRYLKVDFAIDIGSEWII SPKSPDAYYCSGACQFPMPK				
	50	60	70	
SLKPSNHATIQSIVRAVGVIPIGEPECCVPEKMSS				
80	90	100		
LSILFFDENKNVVLKVYPNMTVESACR				

90. A protein comprising the amino acid sequence:

COP1

1	10	20	30	40
LYVDFQRDVGWDDWIIAPVDFDAYYCSGACQFPSAD				
	50	60	70	
HFNSTNHAVVQTLVNNMNPVKVPKCCVPTLSA				
80	90	100		
ISMLYLDENSTVVLKQEMTVVGCGCR				

91. A protein comprising the amino acid sequence:

COP3

1	10	20	30	40
LYVDFQRDVGWDDWIVAPPGYQAFYCSGACQFPSAD				
	50	60	70	
HFNSTNHAVVQTLVNNMNPVKVPKCCVPTLSA				
80	90	100		
ISMLYLDENEKVVVLKQEMVVEGCGCR				

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Cont

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92. A protein comprising the amino acid sequence:

COP4

1	10	20	30	40
LYVDFSDVGWDDWIVAPPGYQAFYCSGACQFPSAD				
	50	60	70	
HFNSTNHAVVQTLVNNMNEGKVPKPCCVPTLSA				
	80	90	100	
ISMLYLDENEKVVVLKNYQEMVVEGCGCR				

93. A protein comprising the amino acid sequence:

COP5

1	10	20	30	40
LYVDFSDVGWDDWIVAPPGYQAFYCHGECPPFLAD				
	50	60	70	
HFNSTNHAVVQTLVNSVNSKIPKACCVPTLSA				
	80	90	100	
ISMLYLDENEKVVVLKNYQEMVVEGCGCR				

94. A protein comprising the amino acid sequence:

COP7

1	10	20	30	40
LYVDFSDVGWDDWIVAPPGYHAFYCHGECPPFLAD				
	50	60	70	
HLNSTNHAVVQTLVNSVNSKIPKACCVPTLSA				
	80	90	100	
ISMLYLDENEKVVVLKNYQEMVVEGCGCR				

95. A protein comprising the amino acid sequence:

COP16

			10	
			PKHHSQRARKKNKN	
1	10	20	30	40
CRRHSLYVDFSDVGWDDWIVAPPGYQAFYCHGECPPFLAD				
	50	60	70	
HFNSTNHAVVQTLVNSVNSKIPKACCVPTLSA				
	80	90	100	
ISMLYLDENEKVVVLKNYQEMVVEGCGCR				

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Cont

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